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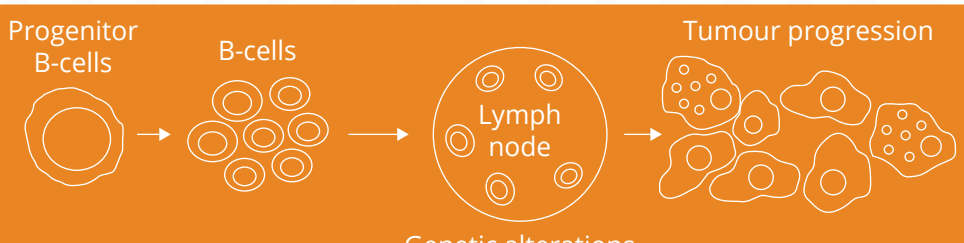
Optimising the Treatment of B-Cell Malignancies

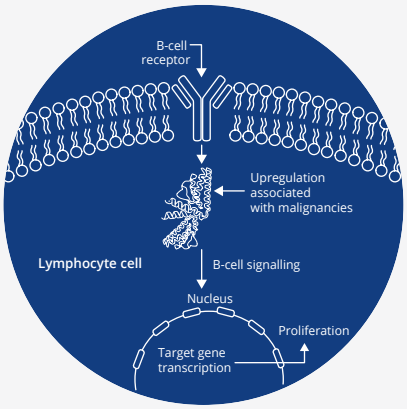
Managing adverse effects and toxicity with prolonged use of Bruton's tyrosine kinase inhibitors

About B-cell malignancies[1]

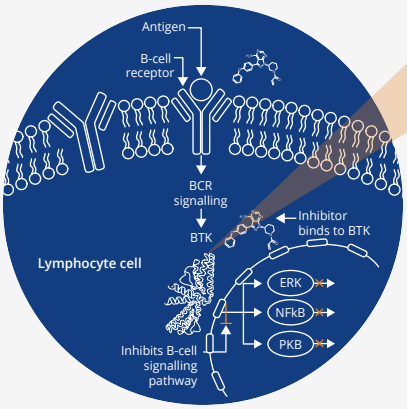


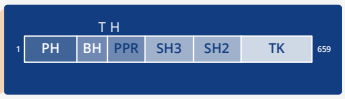
- Heterogenous group of cancers arising from different stages of B-cell differentiation
- Display intra- and inter-patient heterogeneity within each subgroup
- Primary and acquired resistance to treatment is often a major challenge

Bruton's tyrosine kinase inhibitors (BTKis) for B-cell malignancies[2–5]



Bruton's tyrosine kinase (BTK) plays an essential role in B-cell proliferation and activation, and its upregulation is associated with various B-cell malignancies





Domain structure of BTK

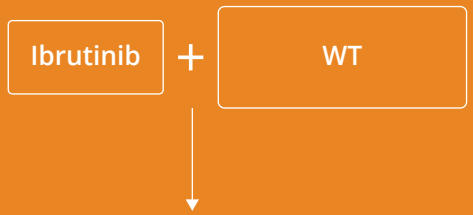
Inhibition of BTK has been shown to be a highly effective treatment strategy in patients with B-cell malignancies

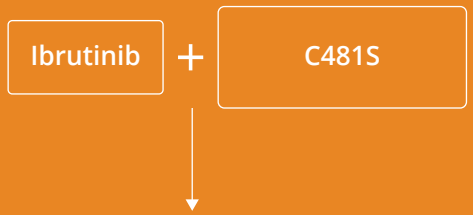
Advantages of BTKis

- Disrupt aberrant mechanisms that drive malignant B-cell pathophysiology
- Deliver better drug response and reduce toxicity
- The number BTKis in the clinic has increased, and currently at least 22 are available

Resistance to BTKis can compromise clinical outcomes and lead to treatment discontinuation

Key mutations driving resistance to BTKis[2,3]





- BTK C481S variant is most frequent and prevents ibrutinib from targeting BTK
- It does so by interfering with the reversible combination of ibrutinib and BTK
- Acquired mutations in BTK are seen in many ibrutinib-resistant cases

ERK: Extracellular signal-regulated kinases • NFkB: Nuclear factor kappa-light-chain-enhancer of activated B-cells • PKB: Protein kinase B • WT: Wild type

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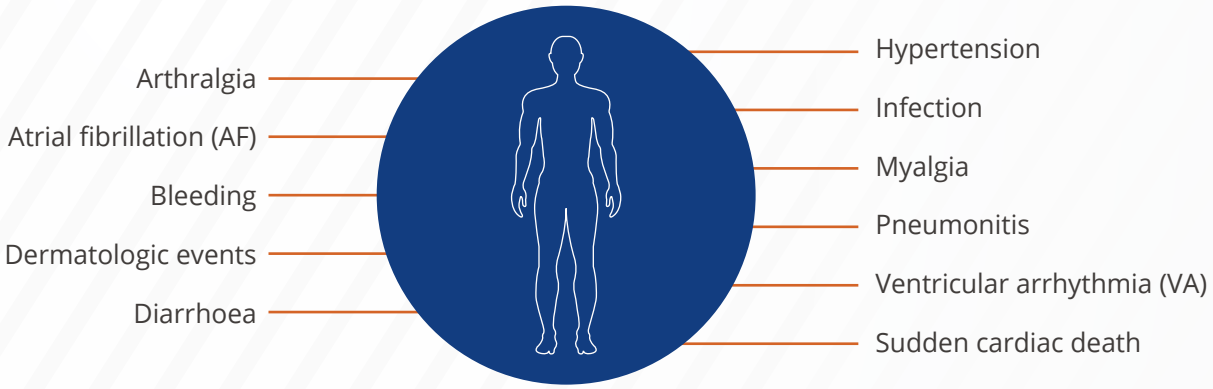
Adverse effects associated with prolonged use of BTKis[6,7]



Of these, arthralgia and infections are often reported early during the course of treatment

BTKis have transformed the treatment of B-cell malignancies, however, adverse effects and complications still need management

Strategies for the management of adverse effects[6,7]

Arthralgia
- Pronounced during early treatment, can resolve over time
- Anti-inflammatory agents with antiplatelet adverse events should be avoided
- Acetaminophen/short pulses of prednisone can be used
- Monitor dosage of BTKi or the transition to alternate BTKi

AF
- Requires collaboration between haematologists and cardiologists and consideration of patients' baseline cardiovascular risk
- Monitoring AF with electrocardiography, TTE, CHA_2DS_2-VASc, and HAS-BLED scores is recommended
- Evaluate other alternative BTKi therapy options, such as conventional chemotherapy or BCL2 inhibitor

Dermatologic events
- Typically self-limiting
- Monitoring dosage of BTKi may help in resolution
- Use oral antihistamines or topical steroids in patients with pruritic symptoms
- Use oils or biotin to treat brittle nails

VA and sudden cardiac death
- Counselling and risks included in patient consent for treatment with BTKis
- Further investigations for symptoms of syncope, dizziness, or palpitations
- Evaluate serious cardiovascular events to gain insights on the incidence and pathophysiology of disease
- Discontinue BTKi treatment in patients with idiopathic VA
- Monitor BTKi treatment until the underlying cause of VA is rectified

Diarrhoea
- Usually self-limiting and resolves on its own
- Consider dietary modifications
- Monitor stool samples in serious cases
- Administer loperamide
- Monitor dosage of BTKi till diarrhoea resolves

Hypertension
- May remain stable over time
- Blood pressure monitoring is recommended
- Should be medically managed in conjunction with a primary physician if diagnosed

Infection
- Monitor the administration of BTKi until infection has resolved
- Treat with anti-infective agents
- Monitor drug interactions with BTKi
- Reduce BTKi dosage

Pneumonitis
- Lung imaging is recommended in case of progressive respiratory symptoms
- Infection evaluation via bronchoscopic culture
- Corticosteroid treatment should be initiated until clinical and radiological resolution of symptoms
- Consider alternative BTKi therapy

Bleeding
- Use of ibrutinib with anticoagulants is not recommended, as it can increase the risk of bleeding
- Patients should be educated on bleeding risk
- Careful maintenance of platelets over 50 x 10^9/L
- Discontinue BTKi if major bleeding event occurs and administer platelet transfusion

BTKi treatment regimens require:

Multidisciplinary input from haematologists, cardiologists, and specialist cardio-oncology services

Personalised and risk-adapted management plans

Further preclinical and clinical research to understand BTKi toxicities

TTE: Transthoracic Echocardiogram

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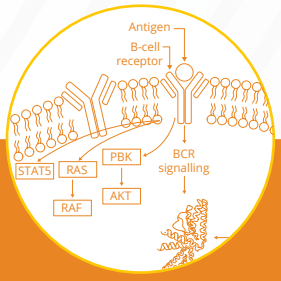
Understanding the mechanisms of resistance to BTKis[8]

Acquired resistance is the main challenge in BTKi therapy, and key mechanisms of resistance include:

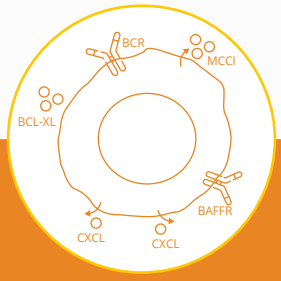
Variants of the drug target arising due to mutations

- Acquired mutations in BH-3-binding domain, C481 binding site, PLCG2, or other relevant BTK variants



Activation of bypass pathways

- Homozygous deletions in CDKN2A/B, BRAF
- Over expression of MYC protein, BCL-XL, and MCL1
  - Resistance to PI3Kδ inhibitors via upregulation of isoforms
  - Selection of clones with mutations in BTG1



Chronic lymphocytic leukaemia (CLL) microenvironment

- Escape signals, anti-apoptotic genes promoted by BAFF and APRIL, and synthesis of pro-survival proteins BCL-XL and MCL1

Treatment strategies to circumvent resistance[8]

Optimising drug dosage

- To reduce toxicity and prevent resistance
- Continue dose-adjustment studies

Employing "drug holidays"

- Indefinite usage can promote intolerable toxicity
- Temporally sequenced treatment with BTKi can help

Use combinatorial therapy to target bypass mechanisms

Leverage drugs that target distinct pathways, show drug synergy, and have limited overlapping toxicity

Incorporate real-time monitoring of patients and improve the design of clinical trials

Overcoming acquired resistance[8]

This can be achieved by:

- Rationalising the design of drug sequencing to secure effective treatment options for relapsed malignancies

- Non-covalent binding of BTKi to a site different from Cys481
- Acting in patients carrying the wild type protein or the C481X variants

- Reversible BTKis can overcome ibrutinib-resistance
- These include vecabrutinib fenebrutinib, nemtabrutinib, and pirtobrutinib

- Bispecific antibodies (BsAb), chimeric antigen receptor-modified (CAR) T-cells, and chimeric targeting molecules

CD3xCD19, a BsAb, can mediate CLL cell killing regardless of sensitivity to ibrutinib or venetoclax

Chimeric molecules present a target to an E3 ligase leading to ubiquination and proteasomal degradation

CAR T-cell therapy is being evaluated given its manageable toxicity profile

Identifying new drug targets

- Identifying new therapies by drug sensitivity screening of patients' tumour cells
- Developing small molecules with novel targets (CDK9, MCL1, and ERK inhibitors)

• APRIL: A proliferation-inducing ligand • BAFF: B-cell activating factor • PLCG2: Phospholipase C gamma 2

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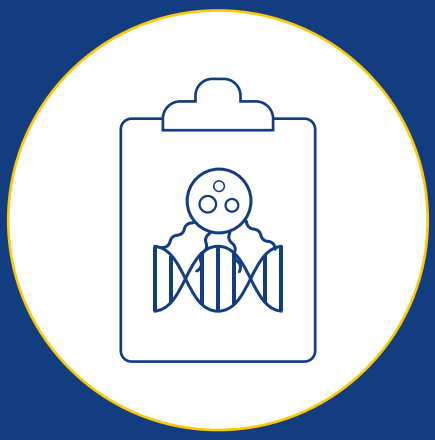
Treatment adaptation to overcome resistance to targeted therapies[8]

Drug Name	Target	Strategy
Ibrutinib	BTK	Drug dosing and temporal sequencing
Duvelisib	PI3K	Temporal sequencing
Ibrutinib + venetoclax	BTK, BCL-2	Fixed duration dosing, combination use, and temporal sequencing
Venetoclax + obinutuzumab	BCL-2, CD20	Fixed duration or combination use
Ibrutinib + venetoclax	BTK, BCL-2	Fixed duration or combination use
Duvelisib + venetoclax	PI3K, BCL-2	Combination
Umbralisib + ibrutinib	PI3K, BCL-2	Combination
Ibrutinib, venetoclax, ublituximab + umbralisib	BTK, BCL-2, CD20, PI3K	Combination
Tafasitamab with idelalisib or venetoclax	CD19, PI3K, BCL-2	Combination
Venetoclax, umbralisib + ublituximab	BCL-2, PI3K, CD20	Combination

BCL-2: B-cell leukaemia/lymphoma 2 • CD20: Cluster of differentiation 20 • PI3K: Phosphoinositide 3-kinase • CD19: Cluster of differentiation 19

Key takeaways

- BTKis are a class of targeted therapeutics for the management of B-cell malignancies, but can also suffer from treatment resistance
- Mutations in BTK and PLCG2 promote the development of progressive CLL after the use of covalent BTKi
- New treatments can reduce inhibitor resistance and improve BTKi therapy outcomes



- This includes the use of non-covalent, reversible BTKis, which can improve and overcome mutations responsible for treatment resistance
- Personalised and risk-adapted plans are needed for managing treatment of patients with B-cell lymphomas
- Complications from BTKi treatment need to be closely monitored and appropriately managed

References

1. Cuenca, M., & Peperzak, V. (2021). Advances and perspectives in the treatment of B-cell malignancies. *Cancers, 13*(9), 2266.
2. Wang, H., Zhang, W., Yang, J., & Zhou, K. (2021). The resistance mechanisms and treatment strategies of BTK inhibitors in B-cell lymphoma. *Hematological Oncology, 39*(5),605–615.
3. Frustaci, A. M., Deodato, M., Zamprogna, G., Cairoli, R., Montillo, M., & Tedeschi, A. (2023). Next generation BTK inhibitors in CLL: evolving challenges and new opportunities. *Cancers, 15*(5), 1504.
4. Smolej, L. (2021). On the road to optimized BTK inhibition in CLL. *Blood, The Journal of the American Society of Hematology, 137*(24), 3313–3314.
5. Estupiñán, H. Y., Berglöf, A., Zain, R., & Smith, C. I. E. (2021). Comparative analysis of BTK Inhibitors and mechanisms underlying adverse effects. *Frontiers in Cell and Developmental Biology, 9*, 630942.
6. Stephens, D. M., & Byrd, J. C. (2019). How I manage ibrutinib intolerance and complications in patients with chronic lymphocytic leukemia. *Blood, The Journal of the American Society of Hematology, 133*(12), 1298–1307.
7. Tang, C. P. S., Lip, G. Y., McCormack, T., Lyon, A. R., Hillmen, P., Iyengar, S.,... & BSH guidelines committee, UK CLL Forum. (2022). Management of cardiovascular complications of Bruton tyrosine kinase inhibitors. *British Journal of Haematology, 196*(1), 70–78.
8. Skånland, S. S., & Mato, A. R. (2021). Overcoming resistance to targeted therapies in chronic lymphocytic leukemia. *Blood Advances, 5*(1), 334–343.

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